Evidence for Concurrent Epidemics of Human Herpesvirus 8 and Human Immunodeficiency Virus Type 1 in US Homosexual Men: Rates, Risk Factors, and Relationship to Kaposi's Sarcoma

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We examined human herpesvirus 8 (HHV-8) seroprevalence and seroincidence among 245 homosexual men from New York City (NYC) and Washington, DC (DC) who have been followed since 1982. An immunofluorescence assay measured antibodies to a latent HHV-8 nuclear antigen. Seroprevalence was 20.4% in 1982; seroincidence was ~15%/year during 1982–1983 but fell sharply thereafter. NYC men had a higher seroprevalence (odds ratio, 3.43; $P < .001$) and seroincidence (rate ratio, 2.13; $P = .01$) than DC men. Risk of Kaposi's sarcoma (KS) was increased in seropositive men (adjusted relative hazard, 3.58; $P = .02$). Among men who were seropositive for both human immunodeficiency virus type 1 and HHV-8, the 10-year cumulative risk of KS was 39%; time from coinfection to KS diagnosis ranged from 15 to 154 months (median, 63.5 months). This study shows an epidemic of HHV-8 among US homosexual men in the early 1980s that was associated with a high risk of developing KS.

The epidemic of Kaposi's sarcoma (KS) in US homosexual men, first noted in 1981 [1, 2], heralded the human immunodeficiency virus type 1 (HIV-1) pandemic. Although hemophiliacs, transfusion recipients, and injection-drug users manifested HIV-1–associated opportunistic infections, KS remained largely confined to homosexual men in developed countries. This epidemiologic pattern led to the hypothesis that the KS epidemic resulted from concurrent epidemics of HIV-1 and a second, unknown, sexually transmitted agent that was common in US homosexual men during the late 1970s and early 1980s [3].

A number of observations suggest that human herpesvirus-8 (HHV-8) may be that second agent. First discovered in 1994 [4], HHV-8 is a γ-herpesvirus that is detectable in nearly all KS tissue specimens [5–9]. The role of HHV-8 as a potentially oncogenic virus is supported by its strong relationship with primary effusion lymphomas [10], its homology with 2 other oncogenic γ-herpesviruses (herpesvirus saimiri and Epstein-Barr virus), and its ability to alter the growth of human endothelial cells in vitro [11]. Previous studies have shown that KS risk is increased in HIV-1–infected persons who have detectable HHV-8 in their peripheral blood lymphocytes [12, 13] or antibodies to HHV-8 in their serum [14–19]. The modes of HHV-8 transmission are not well defined, but seroprevalence studies suggest that HHV-8 is rare in the general population and relatively common in US homosexual men [16, 19].

Our understanding of the temporal relationship between the KS epidemic and HHV-8 infection is limited by a paucity of information on HHV-8 frequency during the earlier years of the HIV-1 epidemic. In the late 1970s and early 1980s, homosexual men frequently had a high number of sex partners and a high risk of sexually transmitted infections, including the newly emergent HIV-1 [20, 21]. In 1982, National Cancer Institute investigators began a prospective cohort study of AIDS incidence in homosexual men from New York City (NYC) and Washington, DC (DC). To clarify the epidemiology of HHV-8 infection and its relationship to KS, we measured antibodies to HHV-8 in serum samples that had been collected longitudinally from these men.

Methods

Subjects. In June 1982, 245 homosexual men were enrolled in a cohort study of patients of primary care physicians in NYC or DC. Patients with AIDS were ineligible, and >90% of other patients agreed to participate [22]. Blood was collected and subjects were interviewed at enrollment and about every 12 months thereafter. DC subjects were not seen in 1983 because of limited resources. Follow-up of many HIV-1–uninfected subjects was discontinued in

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Informed consent was obtained from all subjects who participated in this study, which was approved by an NCI institutional review board.

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1990. Up to that year, 60 subjects had died, and 37 others were no longer available for follow-up. Medical conditions, including KS, were diagnosed on the basis of subject reports, medical records, and death certificates.

Laboratory. Blood specimens were collected in offices of the primary care physicians and shipped to a central repository for processing and cryopreservation. Previous reports describe methods used in this study to perform: HIV-1 EIA and Western blot, hepatitis B virus core antibody, serologic tests for syphilis [22], HIV-1 RNA levels (Amplicor HIV Monitor; Roche Molecular Systems, Branchburg, NJ) [23], and total $CD4^+$ lymphocyte counts [22].

For this analysis, we measured antibodies to latent HHV-8 antigens (LANA) with an immunofluorescence assay (IFA). Serum samples, which had been stored at −70°C, were tested in a blinded fashion for evidence of HHV-8 infection by a method described elsewhere, indirect IFA measuring antibodies to a latency-associated nuclear antigen (anti-LANA) [16]. This assay uses as its substrate isolated nuclei from a HHV-8–latently infected, Epstein-Barr virus–uninfected cell line, BCBL-1. After incubation with 1 : 40 diluted test serum, unbound antibody was washed away, and a secondary antibody, Texas red–conjugated goat anti-human immunoglobulin G, was added. Samples were considered anti-LANA–positive if they give a punctuate nuclear pattern in all BCBL-1 nuclei visualized. All subjects testing anti-LANA positive were blindly retested, along with a random sample of subjects initially testing anti-LANA negative. Samples that gave disparate results (<1% of subjects) were tested a third time, and the majority outcome was taken as final. A sample from each study visit was tested for LANA if the archived serum volume was sufficient.

For most subjects, longitudinal HHV-8 antibody results were consistently negative, consistently positive, or formed a pattern consistent with seroconversion (consistently negative results followed by consistently positive results). We did, however, observe 3 types of deviation from these patterns: a single inconsistent specimen (19 of 191 subjects with ⩾3 HHV-8 results), fluctuation over time (>1 inconsistent result; 9 subjects), or "seroreversion" (consistently positive results followed by consistently negative results; 3 subjects).

Data analysis. Seroprevalence was based on HIV-1 or HHV-8 antibody status at study entry in 1982. In the seroprevalence analysis, we determined odds ratios (ORs), 95% confidence intervals (CIs), and *P* values (Mantel-Haenszel χ^2 test) for dichotomous variables, as well as *P* values (χ^2 test for trend) [24] for variables with more than 2 categories. To determine the relative risk for different specific sexual behaviors, we used logistic regression models [25] to calculate adjusted ORs that controlled for the effect of study site and the number of different sex partners during the period January 1980 through June 1982 (treated as a continuous variable after normalization by $\log_{10}$ transformation).

We determined HIV-1 or HHV-8 seroincidence among subjects who were seronegative for either virus at study entry and who had at least 1 follow-up visit (145 subjects for HIV-1 and 173 for HHV-8). Seroconversion dates were assessed on the basis of the midpoint between the last negative and the first positive antibody test (regardless of subsequent HHV-8 antibody results). Follow-up ended at the earlier of seroconversion, the date of the last negative specimen, or 31 December 1990. We truncated the seroincidence analysis in 1990 because follow-up of many HIV-1 uninfected subjects ended in that year. The median number of specimens examined for HHV-8 antibody during this period was 6 per subject. Of 43 subjects who seroconverted for HHV-8, the number for whom seroconversion was documented by only a single positive specimen was 3.

In the seroincidence analysis, we examined the number of different sex partners during the 6 months prior to study entry (rather than January 1980 through June 1982), to more accurately reflect sexual practices at study entry. We determined incidence rate ratios, 95% CIs, and *P* values [25] for dichotomous variables, as well as *P* values (χ^2 test for trend; PEPI, version 2; USD, Stone Mountain, GA) for variables with >2 categories [26]. We also examined smoothed estimates of the HIV-1 and HHV-8 hazard functions (95% CI) created with flexible parametric methods on the basis of splines [27]. To determine the relative hazard of HHV-8 seroconversion associated with different specific sexual behaviors, we used proportional hazards models (PHREG procedure using SAS/STAT Software, SAS Institute, Cary, NC) [28] to control for the effect of study site and the number of different sex partners during the period January 1982 through June 1982 (treated as a continuous variable after normalization by $\log_{10}$ transformation).

We also created proportional hazards models to assess whether the relative hazard of developing KS was increased among HIV-1–infected subjects who were HHV-8 seropositive. For this analysis, subjects who were HIV-1 seropositive at study entry entered the analysis at that time and others entered at HIV-1 seroconversion. The models included fixed covariates (age at HIV-1 seroconversion and race) and time-dependent covariates ($CD4^+$ lymphocyte count, HIV-1 RNA level, and HHV-8 antibody status); once seropositive for HHV-8, subjects remained so regardless of results from later test dates. We used Kaplan-Meier methods to estimate the KS-free survival period after coinfection with HIV-1 and HHV-8 [29]. For subjects who were seroprevalent for both HIV-1 and HHV-8 on enrollment, we considered coinfection to have occurred at study entry.

Results

Subjects. At study entry, the 245 men ranged in age from 21 to 65 years (median, 33 years; interquartile range, 29–38 years); 215 (87.8%) participants were white, 20 (8.2%) were black, 7 (2.9%) were Hispanic, and 3 (1.2%) were Asian-American. Regarding residence, 160 (65.3%) subjects enrolled in DC, and 85 (34.7%) enrolled in NYC. The number of male sex partners during January 1980 to June 1982 ranged from 1 to >2000 (median, 50 partners; interquartile range, 20 to 140 partners) among the 238 subjects who reported this information.

Seroprevalence and seroincidence of HIV-1 and HHV-8. HIV-1 seroprevalence in 1982 was 34.0%. The seroprevalence was greater in men from NYC (48.8%) than in those from DC (26.3%; OR, 2.68; 95% CI, 1.55–4.63; $P = .001$). HIV-1 seroincidence during 1982–1990 was 6.3 (per 100 person-years). The rate was similar in NYC (5.8) and DC (6.5), but it varied markedly over time, as it was 9.7 during 1982–1986 and 0.0 during 1987–1990 ($P < .001$). The HIV-1 hazard curve (figure 1, top)

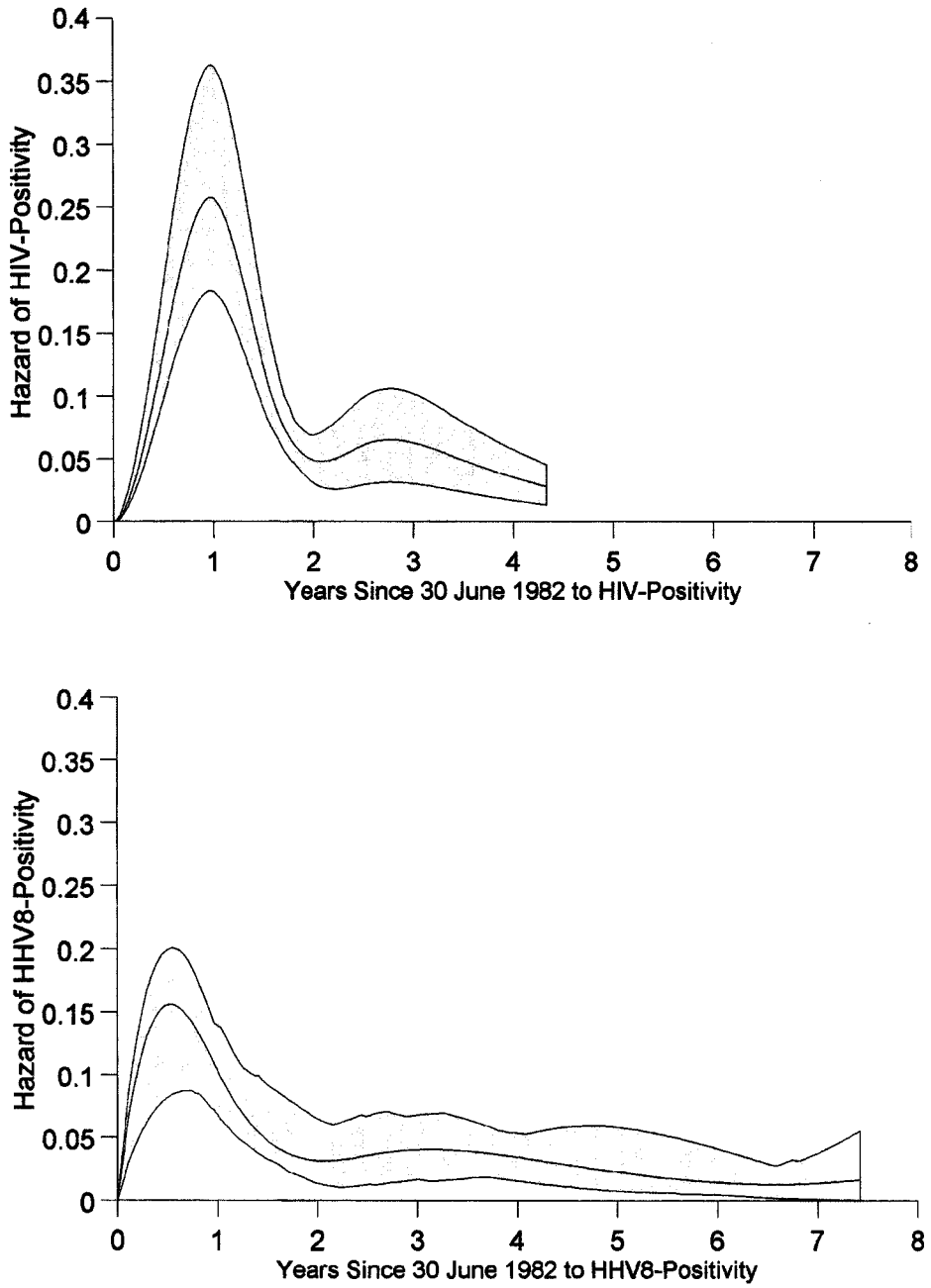

Figure 1. Smoothed hazard curves and 95% confidence intervals for human immunodeficiency virus type 1 (HIV-1; top) and human herpesvirus 8 (HHV-8; bottom) seroconversion among initially seronegative subjects, by time since entering study in June 1982.

indicates that HIV-1 seroincidence peaked at about 25% per year during the first year of the study, then fell sharply.

HHV-8 seroprevalence in 1982 was 20.4%. As with HIV-1, HHV-8 seroprevalence differed markedly by the site of enrollment (NYC, 34.1%; DC, 13.1%; OR, 3.43; 95% CI, 1.84–6.39; $P < .001$), and this difference persisted after we adjusted for number of sex partners (adjusted OR, 2.82; 95% CI, 1.43–5.76; $P = .003$). HHV-8 seroincidence during 1982–1990 was 5.0, but the rate was considerably higher during 1982–1986 (6.7) than during 1987–1990 (1.1; incidence rate ratio, 6.14; 95% CI 1.96–31.03; $P < .001$) and higher in men from NYC (8.3) than in those from DC (3.9; rate ratio, 2.13; 95% CI, 1.17–3.89; $P = .01$). With a pattern similar to that for HIV-1, the HHV-8 hazard peaked (15%/year) during the first year of the study and then fell sharply (figure 1, bottom).

HHV-8 risk factors. HHV-8 seroprevalence differed markedly by the number of male sex partners during the 2.5 years prior to study entry (figure 2*A*). For example, 37.2% of men

reporting ⩾200 partners were seropositive for HHV-8, compared with 7.8% of those reporting ⩽16 partners ($P < .001$, χ^2 for trend). HHV-8 seroincidence was also associated with the number of sex partners, ranging from 18.2 in those with 50 or more partners during the first 6 months of 1982 (figure 2*B*) to 0.9 in those with 0–2 partners ($P < .001$, χ^2 for trend). The relationship between HIV-1 frequency and the number of male sex partners was similar. For example, 58.1% of men who reported ⩾200 partners during the 2.5 years prior to study entry were seropositive for HIV-1, compared with 11.8% of those with ⩽16 partners ($P < .001$, χ^2 for trend). HIV-1 seroincidence was also strongly associated with the number of sex partners, ranging from 0.8 among 20 subjects with 0–2 partners during the 6 months before enrollment to 54.8 among 10 men reporting ⩾50 partners during that period ($P < .001$, χ^2 for trend).

HHV-8 seropositivity was increased in men who had evidence of other sexually transmitted infections (table 1). Although men given a diagnosis of gonorrhea, nongonococcal urethritis, syphilis, or herpes genitalis during the 12 months prior to enrollment had only a moderately increased HHV-8 seroprevalence, HHV-8 seroprevalence was significantly elevated in men who reported amoebiasis during that period (OR 2.73; 95% CI, 1.30–7.23), as well as in men with serologic evidence of HIV-1 infection (OR, 4.98; 95% CI, 2.58–9.62), syphilis (OR, 3.24; 95% CI, 1.71–6.13), or hepatitis B virus infection (OR, 3.14; 95% CI, 1.31–7.52).

To determine more exactly how HHV-8 was acquired by these men, we examined the relationship between the frequency of specific sexual behaviors and HHV-8 seroprevalence (table 2). To control the potential confounding of these relationships by the number of different sex partners or by study site, we used logistic regression models to adjust for these variables. Comparing subjects who reported no episodes of a behavior to subjects in the highest category, the adjusted odds ratio for HHV-8 seroprevalence exceeded 1 for all behaviors except receptive fellatio. ORs were elevated by >3-fold for receptive anal intercourse (adjusted OR, 4.11; 95% CI, 0.99–16.98), insertive anal intercourse (adjusted OR, 5.33; 95% CI, 0.99–28.53), insertive anilingus (adjusted OR, 5.52; 95% CI, 1.27–23.96), and insertive fisting (adjusted OR, 8.13; 95% CI, 2.20–30.02). Similar results were obtained when we controlled the analysis of each specific behavior for the frequency of every other behavior in a pairwise fashion (data not presented). We also created logistic regression models that examined the overall relationship between a behavior and HHV-8 seroprevalence by treating each sexual behavior variable as a set of ordered categories, similar to a test for trend (table 2). In this second set of models, we found statistically significant associations between HHV-8 seroprevalence and the following: receptive anal intercourse ($P = .03$), insertive anilingus ($P = .01$), and insertive fisting ($P = .007$).

Similarly, we examined the relationship between HHV-8 seroincidence and these 8 sexual behaviors in proportional hazards models (table 2). The seroincidence data provided less statistical

Table 1. Prevalence of human herpesvirus 8 infection by evidence of other sexually transmitted infections.

	Positive/total (%)	OR	95% CI	*P*
Diagnosed with a STD[a]				
Yes	35/155 (22.58)	1.46	0.75−2.85	.3
No	15/90 (16.67)			
Diagnosed with amoebiasis				
Yes	7/18 (38.89)	2.73	1.30–7.23	.04
No	42/222 (18.92)			
HIV-1 antibodies (1982)				
Positive	32/83 (38.55)	4.98	2.58–9.62	.001
Negative	18/161 (11.18)			
Hepatitis B core antibodies (1982)				
Positive	44/177 (24.86)	3.14	1.31–7.52	.01
Negative	6/63 (9.52)			
Syphilis serology (1982)				
Positive	23/63 (36.51)	3.24	1.71–6.13	.001
Negative	27/179 (15.08)			

NOTE. For diagnoses, reporting period is the 12 months prior to enrollment. CI, confidence interval; OR, odds ratio; STD, sexually transmitted disease.
[a] Gonorrhea, nongonococcal urethritis, syphilis, or herpes genitalis.

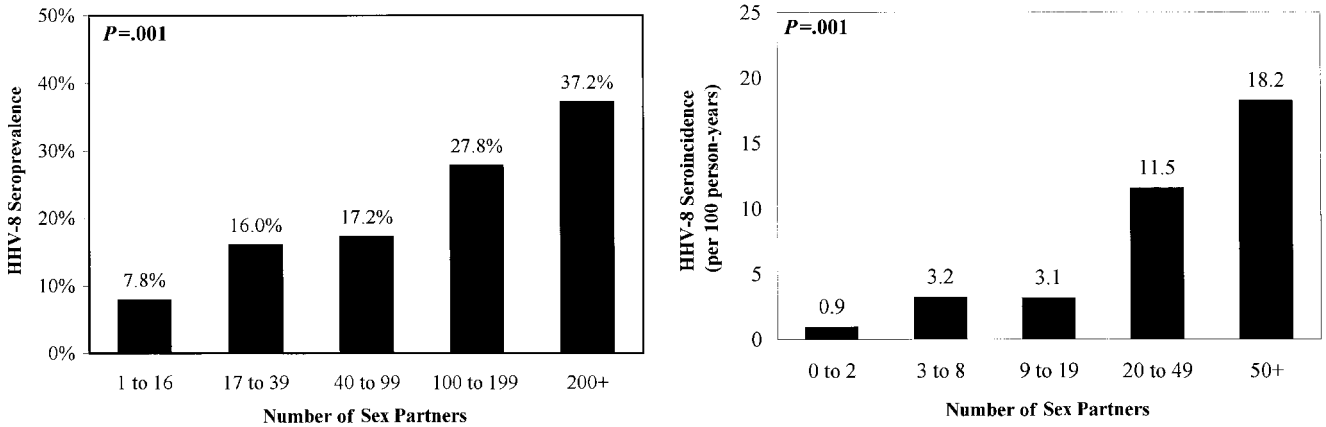

Figure 2. *(A)* Seroprevalence of human herpesvirus 8 (HHV-8) at study entry in 1982, by number of different male sex partners during 2.5 years prior to study entry. *(B)* Seroincidence of HHV-8, by number of different male sex partners during 6 months prior to study entry. $P < .001$ for both comparisons; χ^2 for trend.

Table 2. Seroprevalence (per 100 subjects) and seroincidence (per 100 person-years) of human herpesvirus 8 infection by frequency of sexual practices during 12 months prior to enrollment.

	Seroprevalence				Seroincidence			
	Subjects	Rate	Adjusted[a] OR (95% CI)	P[c]	Subjects	Rate	Adjusted[b] HR (95% CI)	P[c]
Receptive fellatio								
0	17	29.4		.7	11	4.10		.8
1–4	42	14.3			30	5.71		
5–9	43	16.3			33	4.80		
10–19	57	19.3			41	2.18		
20–49	47	21.3			33	7.65		
50+	29	31.0	0.65 (0.15–2.80)		18	8.20	0.40 (0.07–2.26)	
Receptive anal intercourse								
0	28	10.7		.03	22	0.00		.06
1–4	44	15.9			29	8.00		
5–9	33	9.1			28	4.52		
10–19	52	28.9			34	3.43		
20–49	37	13.5			30	7.86		
50+	42	38.1	4.11 (0.99–16.98)		23	8.49	ND	
Insertive fellatio								
0	15	13.3		.3	10	2.30		.1
1–4	34	14.7			27	3.10		
5–9	40	15.0			31	1.84		
10–19	55	23.6			37	5.58		
20–49	56	19.6			39	6.85		
50+	35	34.3	2.03 (0.35–11.83)		21	11.55	1.23 (0.14–11.13)	
Insertive anal intercourse								
0	28	7.1		.1	20	3.78		.02
1–4	41	14.6			30	3.27		
5–9	38	23.7			28	1.23		
10–19	45	26.7			30	7.72		
20–49	47	17.0			34	7.60		
50+	37	32.4	5.33 (0.99–28.53)		24	7.37	1.13 (0.32–3.96)	
Insertive anilingus								
0	83	14.5		.01	61	3.37		.01
1–4	48	14.6			36	3.84		
5–9	43	23.3			31	5.17		
10–19	29	17.2			23	6.40		
20–49	21	38.1			11	12.54	2.97 (1.16–7.54)[d]	
50+	12	58.3	5.52 (1.27–23.96)		4	30.24		
Receptive anilingus								
0	51	17.7		.2	33	2.75		.03
1–4	55	12.7			45	2.80		
5–9	43	11.6			35	5.45		
10–19	46	32.6			30	4.66		
20–49	28	28.6			18	22.51	2.95 (0.88–9.90)[d]	
50+	13	38.5	1.28 (0.29–5.67)		5	3.92		
Insertive fisting								
0	182	15.9		.007	136	4.92		.7
1–4	29	24.1			20	5.28		
5–9	14	28.6			9	4.57	0.61 (0.18–2.03)[d]	
10+	13	69.2	8.13 (2.20–30.02)		3	7.91		
Receptive fisting								
0	212	18.9		.1	152	4.65		.4
1–4	14	28.6			9	10.96	1.61 (0.67–3.86)[d]	
5–9	6	33.3	2.23 (0.64–7.79)[d]		4	5.96		
10+	6	50.0			3	6.98		

NOTE. CI, confidence interval; HR, hazard ratio; OR, odds ratio; ND, not determined.

[a] OR compares highest with lowest category and is adjusted for study site and no. of different sex partners (1/80–6/82).

[b] HR compares highest with lowest category and is adjusted for study site and no. of different sex partners (1/82–6/82).

[c] P values are based on logistic regression (or proportional hazards models), in which behavioral variables are treated as ordered categories. These models are adjusted for study site and no. of different sex partners.

[d] Categories were combined to create highest category with ⩾10 subjects.

power than the seroprevalence data, but 2 findings were clearly consistent with the seroprevalence analysis: HHV-8 seroincidence was associated with insertive anilingus, but not with receptive fellatio. Missing data on sexual behaviors during the period of peak HHV-8 seroincidence precluded examining the relationship between these behaviors and HHV-8 seroincidence in a time-dependent fashion.

There was no consistent relationship between age and HHV-8 seroprevalence (data not shown), but subjects who were aged 20–24 years at study entry had a much higher HHV-8 incidence (15.3) than older subjects. There was also an overall trend toward a greater HHV-8 seroincidence in younger men ($P = .03$, χ^2 for trend).

HHV-8 seropositivity and the development of Kaposi's sarcoma. Since no HIV-1–uninfected men developed KS, we restricted the analysis of the relationship of HHV-8 to KS to the 134 HIV-1 seropositive subjects. The relative hazard of developing KS was 3.04 (95% CI, 1.29–7.18; $P = .01$) when HHV-8 seropositive subjects were compared with seronegatives; the relative hazard rose modestly (3.58; 95% CI, 1.65–9.53; $P = .02$) after we adjusted for $CD4^+$ lymphocyte counts and HIV-1 RNA levels. Of the 31 men who were given a diagnosis with KS, 7 were never HHV-8 seropositive. Of these, 1 was persistently HHV-8 seronegative before and after the development of KS, and 6 were diagnosed with KS after the date of the last serum specimen that was available for testing (median time from the last HHV-8 test to KS diagnosis, 13 months; range, 4–27 months). No subject seroconverted for HHV-8 after developing KS.

To assess the temporal relationship between HIV-1/HHV-8 coinfection and the development of KS, we examined the KS-free survival time among the 75 men who were seropositive for both viruses in a Kaplan-Meier analysis (figure 3). The 10-year KS-free survival proportion was 61%, and the median time to KS among the 24 men who developed KS was 63.5 months (range, 15–154 months). Among 43 dually seropositive men who seroconverted for HIV-1, HHV-8, or both viruses while enrolled in the study, 10-year KS-free survival was 64%; the median time to disease among the 13 men who developed KS was 53 months (range, 15–130 months). The KS incubation period distribution among the 25 subjects who seroconverted for HHV-8 after becoming seropositive for HIV-1 did not differ from that of the 13 men who seroconverted for HIV-1 after becoming seropositive for HHV-8 ($P > .5$).

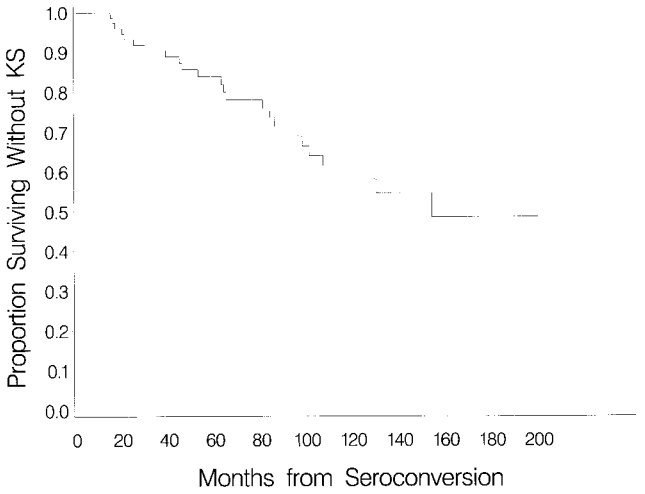

Figure 3. Proportion of subjects surviving without Kaposi's sarcoma (KS) after becoming seropositive for human immunodeficiency virus type 1 and human herpesvirus 8. Date of dual infection was assumed to be enrollment date for subjects who were dually infected at study entry.

Discussion

The patterns of seropositivity to HHV-8 and to HIV-1 were very similar in this cohort. For both viruses, seroprevalence was high in June 1982 (20.4% for HHV-8 and 34.0% for HIV-1), and the estimated relative hazard of seroconversion peaked during 1983. The pattern of HHV-8 frequency that we observed is consistent with national estimates of HIV-1 incidence, as a statistical reconstruction of the HIV-1 epidemic among US homosexual men as a whole has indicated that HIV-1 incidence peaked in about 1984 and then declined sharply [30]. The drop in HIV-1 incidence among homosexual men has been attributed to changes in sexual practices in response to the AIDS epidemic and early infection of the most sexually active men [30]. As we found considerable evidence that HHV-8 is sexually transmitted, the same factors may account for the decline in HHV-8 seroincidence observed in this cohort. HHV-8 seroincidence among men with $\geqslant$50 partners during the 6 months prior to enrollment was 20$\times$ greater than that for men with 0–2 partners; HHV-8 prevalence was elevated in men with evidence of other sexually transmitted infections, consistent with results from other studies [16, 19]. Our study, therefore, provides strong evidence that a sexually transmitted epidemic of HHV-8 occurred among US homosexual men during the early 1980s, concurrent with the epidemic of HIV-1 in that population.

At study entry in 1982, HHV-8 was much more common in men enrolled in NYC (34.1%) than those from DC (13.1%), and the disparity was not explained by differences in sexual activity during the preceding 2.5 years. HHV-8 seroincidence rates were consistent with the seroprevalence data, as men from NYC were about 2.5$\times$ more likely to have seroconverted between 1982 and 1990. These data suggest that the HHV-8 epidemic gained a foothold in NYC before becoming common in DC. Given the putative etiologic association between HHV-8 and KS, this geographic pattern is consistent with NYC's role as an epicenter for very early cases of AIDS-associated KS [1, 2].

Our results are generally consistent with recent studies of HHV-8 in European homosexual men. In a Danish cohort, the

HHV-8 prevalence was 21.1% in late 1981, and HHV-8 seroincidence peaked in 1981–1982 [31]. In men from Amsterdam, the prevalence of HHV-8 in 1984 was 20.9%, and the subsequent seroincidence was relatively flat [32], suggesting that the HHV-8 epidemic in that population may have peaked by 1984. Together, these studies and ours suggest that an international epidemic of HHV-8 occurred among homosexual men at about the time of onset of the AIDS epidemic.

To investigate possible mechanisms of sexual transmission, we looked at the relationship between HHV-8 frequency and specific sexual behaviors. Although this analysis was limited by the fact that most men reported multiple behaviors and by the presence of relatively few subjects in some behavioral categories, we can conclude that HHV-8 seropositivity was not associated with receptive fellatio. It is, therefore, unlikely that oral-pharyngeal exposure to semen was a common mechanism of HHV-8 transmission in this cohort. Behaviors involving rectal mucosal exposure, especially insertive anilingus, were associated with HHV-8 acquisition. This result is consistent with earlier studies that examined the relationship between specific sexual behaviors and the risk of KS [33, 34].

Among HIV-1–infected men, HHV-8 seropositive subjects were about 3.5× more likely to develop KS than HHV-8 seronegative subjects. This relative risk is about 50% higher than the 2.4-fold relative risk reported for a baseline HHV-8 LANA result alone [19], possibly because we examined HHV-8 serostatus longitudinally in the present study. We also found that more than one-third of the men who were seropositive for both HIV-1 and HHV-8 developed KS within 10 years. We did not confirm a previous report that seroconversion for HHV-8 during HIV-1 infection leads to more rapid development of KS [32], but our study may have been too small to detect that difference. Our findings do indicate that HIV-1–infected patients who are also infected with HHV-8 are at high relative and absolute risk of developing KS. If therapies to prevent KS become available in the future, HHV-8 screening of high-risk groups and prophylactic treatment of HHV-8 seropositive individuals may be indicated.

Some limitations of this study should be considered. Although HHV-8 is found in KS tissue specimens of almost all patients with KS, a previous (cross-sectional) study of KS patients found that only 83% were LANA positive [16]; fluctuating longitudinal LANA results among subjects in this study may be another indication that LANA sensitivity is <100%. As a result, we probably underestimated the prevalence and incidence of HHV-8 infection in this cohort and, assuming that LANA sensitivity is unlinked to sexual behaviors or residence in NYC, underestimated the association between HHV-8 and those variables [35]. Currently available HHV-8 antibody assays have limitations [36], but our study unequivocally demonstrates LANA's value as an epidemiologic tool.

The time from dual seropositivity (HIV-1 and HHV-8) to KS diagnosis in our subjects ranged from slightly over 1 year to almost 13 years (median, 5.3 years), but these data should be interpreted with some caution. Many of the men who were coinfected with HIV-1 and HHV-8 were seropositive for both viruses at study entry. Our dating of coinfection from study entry in these men tends to underestimate the incubation period to KS. Our failure to detect HHV-8 antibodies in 7 of 31 subjects who were given a diagnosis of KS also limited our estimates of the KS incubation period. Although this finding may reflect LANA insensitivity, 6 of the 7 subjects were diagnosed after the date of the last specimen available for serologic testing. The time from the last HHV-8 test to KS diagnosis was fairly short for these subjects (range, 4–27 months), and if subjects with shorter incubation periods were excluded from our analysis, we may have overestimated the median time from HHV-8/HIV-1 seropositivity to KS diagnosis. However, while additional data and, perhaps, a more sensitive assay are needed to determine this incubation period precisely, we have shown that the time from dual seropositivity to the development of KS varies widely and frequently exceeds a decade.

In conclusion, we found evidence that concurrent epidemics of HIV-1 and HHV-8 were present among US homosexual men during the early 1980s and that the incidence of HHV-8 subsequently slowed dramatically in parallel with the incidence of HIV-1. Our results also indicate that the risk of KS among men who are infected with both HHV-8 and HIV-1 is high, at least in the absence of effective antiretroviral therapy. Future studies should focus on the mechanisms by which HHV-8 infection causes KS and on therapies to prevent KS in patients infected with this virus.

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